

In re: Foster et al.  
Application No.: 10/518,471  
Filed: December 17, 2004  
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### **REMARKS**

Claims 1, 3, 6, 7 and 11-16 are pending in this application. Claim 1 is amended herein for clarity and to more particularly define the invention. Support for this amendment is found in the language of the original claims and throughout the specification. It is believed that no new matter is added by this amendment and its entry and consideration are respectfully requested. In light of this amendment and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

#### **Rejection under 35 U.S.C. § 103(a).**

The Office Action states that claims 1, 3, 6-7 and 11-16 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Uhlen et al. (U.S. Patent No. 6,831,161) in view of James et al. (U.S. Patent Application No. 2003/0162225). Specifically, the Office Action alleges that Uhlen et al. teaches cleaning and sanitizing chromatographic columns by washing with 0.1 to 1.0M NaOH in combination with NaCl for removing prions. The Office Action further alleges that Uhlen et al. teaches the invention substantially as claimed with the exception of the concentration of NaCl solution. The Office Action alleges that James et al. teaches elution of PrP from a chromatography column using 1.5M NaCl and concludes that it would have been obvious to a person of ordinary skill in the art to have modified the NaCl of Uhlen et al. to include 1.5M NaCl as taught by James et al., for the purpose of eluting PrP from the chromatography column.

Claim 1 is amended herein to recite a method of cleaning a substrate of chromatographic materials in order to remove adsorbed prion infectivity, comprising washing the substrate with a concentrated salt solution consisting of an aqueous solution of sodium chloride, wherein the salt solution comprises a concentration of at least 1.0M.

Uhlen et al. fails to teach sodium chloride for removal of prions. Instead, Uhlen

et al. states that NaOH in combination with NaCl is a recognized standard for cleaning and sanitizing separation media and systems (Uhlen et al., column 2, lines 8-10). The only mention of prions in Uhlen et al. is a statement that an applied 0.1-1.0M NaOH solution is able to remove among other contaminating agents, prions (Uhlen et al., column 2, lines 8-10). This is correct and, in fact, NaOH is one of the recognized treatments for removing prions (preferably a 1N solution of NaOH for 1 hour at 20°C). In support of this contention, enclosed herewith, is an EEC regulatory document (*Biologicals* 20:155-158 (1992); Appendix D). This is an approved EEC regulatory document and refers to removal of infectivity during a production process using 1N NaOH. Thus, it is NaOH alone, not NaCl alone or NaOH in combination with NaCl, that was recognized as being suitable for removal of prions. As discussed above, it is the use of NaOH alone that Uhlen et al. mentions for removal of prions. Accordingly, Uhlen et al. fails to suggest or teach the removal of prions with NaCl as taught in claim 1 of the present invention.

Further, James et al. fails to remedy the deficiencies of Uhlen et al. James et al. refers to the treatment of recombinant normal prion proteins and not infectious prions (i.e., abnormal prions), which are the subject of the present invention.

In further support of these arguments, applicants provide herewith a Declaration under 37 C.F.R. § 1.132 of Dr. Ian R. MacGregor (hereinafter "the MacGregor Declaration; Appendix A), wherein Dr. MacGregor discusses the differences between normal prion proteins and abnormal infectious prion proteins. Dr. MacGregor points out that it is well known in the art that there are significant structural differences between normal prion proteins and abnormal prion proteins, and indeed, it is these tertiary structural differences that give rise to the abnormal infectious behavior of infectious prion proteins. Thus, behavior, which could be ascribed to normal prion proteins, could not be regarded as a good basis for treatment of abnormal prion proteins.

In addition, two further papers are enclosed (Appendix E): (1) Bennion et al. ("Protein Conformation and Diagnostic Tests: The Prion Protein," *Clinical Chemistry* 48:2105-2114 (2002)) and (2) Riesner, (Biochemistry and Structure of PrP<sup>C</sup> and PrP<sup>SC</sup>, *British Medical Bulletin* 66: 21-33 (2003)). The Bennion et al. reference describes what is meant by primary, secondary and tertiary structures of proteins (introductory paragraph) and also includes, in Figures 1 and 2, molecular models showing postulated changes in tertiary structure which are involved in the mutation of a normal prion protein to an infectious prion protein. In essence, normal and abnormal prion proteins share common primary and secondary structures but the differences in three dimensional configuration (i.e., tertiary structure) give rise to widespread and fundamental differences in the properties of the proteins, including the fact that infectious prion proteins tend to aggregate while normal prion proteins tend to be present as monomers and that normal prion proteins are non-infectious whereas abnormal prion proteins may be highly infectious. Accordingly, one of ordinary skill in the art desiring to remove infectious prion proteins from chromatographic materials would not look to James et al. for guidance because James et al. addresses only normal, non-infectious prion proteins.

Furthermore, James et al. fails disclose the use of a concentration of at least 1.0M NaCl for washing a substrate as taught in claim 1 of the present invention. James et al. discusses the elution of recombinant normal prion proteins from a chromatography column using a buffer C supplemented with 1.5M NaCl (James et al., page 4, paragraph 0045, emphasis added). However, the reference to the 1.5M NaCl is the concentration of the sodium chloride before it is added to the buffer C. Thus, once the sodium chloride is mixed with the buffer C, the sodium chloride concentration is significantly lower than 1.5M. In fact, if equal volumes of 1.5M NaCl and buffer C were mixed the concentration of NaCl would fall to 0.75M, which is outside the presently claimed range of at least 1.0M recited in claim 1. Since the NaCl is described as supplementing the buffer C, one would not expect its volume to constitute even one-

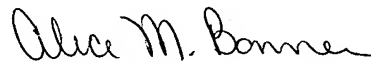
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half of the whole. Thus, James does not disclose the use of sodium chloride concentrations of at least 1.0M as taught by claim 1 of the present invention.

In view of the foregoing, Applicants believe that the points and concerns raised by the Examiner in the Action have been addressed in full, it is respectfully submitted that this application is in condition for allowance. Should the Examiner have any remaining concerns, it is respectfully requested that the Examiner contact the undersigned Attorney at (919) 854-1400 to expedite the prosecution of this application to allowance.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of \$910.00 (\$790.00 as fee for a large entity for a Request for Continued Examination and \$120.00 as a fee for one-month extension of time). This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,



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Amelia Tauchen